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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/751,299	12/28/2000	Mark Madden	DIVER1440-2	8629

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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/751,299	MADDEN ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-21 and 23-50* is/are pending in the application.

4a) Of the above claim(s) *18-21 and 25-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-17,23,24 and 31-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/6/04, 8/6/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicant's submission filed on July 6, 2004 has been entered.

2. In response to the previous Office action, a Final rejection (mailed on October 1, 2003), Applicants filed a response and amendment received on July 6, 2004. Said amendment cancelled Claims 9 and 22, amended Claims 1-3, 5, 8, 10, 11, 14, 23, 24, 31-33, 36, 38-42, and 44 and added new Claims 45-50. Thus, Claims 1-8, 10-21, and 23-50 are pending in the instant Office action.

Election

3. Claims 1-8, 10-21, and 23-49 are pending in the instant application. Claims 18-21 and 25-30 remain withdrawn from consideration as non-elected inventions. Claims 1-8, 10-17, 23, 24, and 31-50 will be examined herein.

The Examiner notes that the elected invention is a method. Thus, all product claims still pending in the instant application are ***not*** subject to rejoinder.

Priority

4. As previously noted, the instant application is granted the benefit of priority for the U.S. Provisional Application Nos. 60/173,609 and 60/254,414 filed on December 29, 1999 and December 7, 2000, respectively.

Information Disclosure Statement

5. The information disclosure statements filed on August 6, 2003 and July 6, 2004 have been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copies.

Maintained - Objections to the Specification

6. Previous objection to the amendment filed July 22, 2003 under 35 U.S.C. § 132 because it introduces new matter into the disclosure is maintained. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that the material added was inherently contained in the original application because the sequences of the enzymes BD 1911 and BD 1912 are expressly disclosed; however, this is not exactly correct. While SEQ ID NOs: 1-4 are disclosed, they are not disclosed as encoding (or being) the enzyme BD 1911 or BD 1912. The amendment to the specification adds just this fact. But this fact cannot be gleaned from the specification as originally filed.

BD 1911 and BD 1912 are described in Example 1 and are not described by means of sequence information, no encoding DNA, no protein sequence, and no vector from which expression was achieved. Contrary to Applicant's arguments, these SEQ ID NOs are *not* mentioned whatsoever in Example 1. The specification on page 6, lines 6-9 describes the

activities of the polypeptides of SEQ ID NOs: 2 and 4 but does not describe SEQ ID NOs:2 and 4 as BD 1911 or BD 1912. Therefore, the instant objection is maintained.

As previously noted,

> "The definition of the enzyme preparations as particular SEQ ID NOs is not supported in the specification as originally filed. While the specification contained a sequence listing in diskette form on the day of filing, December 28, 2000, the computer readable sequence listing referred to SEQ ID NOs:1-4 only as "description of unknown organism: obtained from an environmental sample" and not specifically as BD1911 or 1921. Thus, the correlation between the enzyme preparations and particular SEQ ID NOs is considered new matter."

Withdrawn - Claim Rejections - 35 U.S.C. § 112, second paragraph

7. Previous rejection of Claims 2-10 under 35 U.S.C. § 112, second paragraph, as being indefinite for the meaning of the "*" by the center "C" is withdrawn by virtue of Applicant's amendment to the structure in Claim 2.

8. Previous rejection of Claims 22-24 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrases "amino acid sequence as set forth in SEQ ID NO:2 or SEQ ID NO:4" and "a nucleic acid sequence as set forth in SEQ ID NO:1 or SEQ ID NO:3" is withdrawn by virtue of Applicant's amendment.

Withdrawn - Claim Rejections - 35 U.S.C. § 112, first paragraph

9. Previous rejection of Claims 1-17 and 31-37 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicant's amendment. For all the method claims using nitrilases, both structure (either exactly SEQ ID NOs:2 or 4 or some percent identity to

SEQ ID NOs:2 or 4) and function (inherent in exactly SEQ ID NO:2 or 4 and required by the word "nitrilase" where the structure is varied).

10. Previous rejection of Claims 22-24 and 38-43 under 35 U.S.C. § 112, first paragraph, new matter, as failing to comply with the written description requirement for the term "enzymatically active fragments" is withdrawn. Applicant has pointed out the reference to active fragments in the specification that supports the previous amendment to the claims.

11. Previous enablement rejections under 35 U.S.C. § 112, first paragraph will be addressed below in new rejections and response to arguments.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

12. Previous rejection of Claims 1-4, 6, 11-17, 31, and 33-36 under 35 U.S.C. § 102(b) as being anticipated by Wakamoto *et al.* as evidenced by Iyer *et al.* is withdrawn by virtue of Applicant's amendment requiring specific structure for the nitrilases used in the claimed methods, which structure is not taught by the prior art.

13. Previous rejection of Claim 32 under 35 U.S.C. § 102(b) as being anticipated by Wakamoto *et al.* is withdrawn by virtue of Applicant's amendment requiring specific structure for the nitrilases used in the claimed methods, which structure is not taught by the prior art.

14. Previous rejection of Claims 32 and 37 under 35 U.S.C. § 102(b) as being anticipated by Bhalla *et al.* is withdrawn by virtue of Applicant's amendment requiring specific structure for the nitrilases used in the claimed methods, which structure is not taught by the prior art.

NEW ISSUES

Objections to the Claims

15. Claim 1 is objected to for improper punctuation. In the last line of the claim, the comma after "SEQ ID NO:2," is inappropriate since only two items are listed.

16. Claim 23 is objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The added limitation further defining the sequence that encoded SEQ ID NOs:2 or 4 from the parent claim does not further limit Claim 1 because it does not change the nature of SEQ ID NOs: 2 or 4.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 1-8, 10, 23, 24, 38-43, 45-46, and 49-50 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "reaction components" is wholly unclear. Initially with the use of the nitrilase, using nitrilase substrate(s) is implied; this would include a nitrile and water wherein the nitrile is hydrolyzed to a carboxylate (the α-substituted carboxylic acid in the preamble) and ammonia. However, then in Claim 47 (for the

case of Claim 1 and Claim 48 for the case of Claim 24), reaction components are otherwise limited. The specification does not describe this term except by means of the example, which includes only benzaldehyde, KCN, and NH_4Cl as components to produce phenylglycinonitrile which is further hydrolyzed by the nitrilase to produce phenylglycine. Clarification of what "reaction components" encompass is required.

18. Claims 44 and 50 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "the same enzymatic activity as nucleic acid sequence from which it varies" is confusing because the activity being defined is a polypeptide, which does not have the activity of a nucleic acid sequence. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1-8, 10-17, 23, 24, 33, 38-43, and 45-48 are rejected under 35 U.S.C. § 112, first paragraph, enablement, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Methods producing **enantiomerically pure** α-substituted carboxylic acids would require undue experimentation to make.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification teaches using enzymes BD 1911 and BD 1921, which have been described during prosecution as SEQ ID NOs:2 and 4, respectively, to produce phenylglycine from phenylglycinonitrile (see Example 1, pages 77-78). In a declaration by Inventor Chaplin (filed July 22, 2003), it is attested that SEQ ID NOs: 2 and 4 have been recombinantly expressed and combined separately with phenylglycinonitrile (which can be produced from benzaldehyde, KCN, and NH_4Cl in a Strecker reaction (see page 77) to produce (S)-phenylglycine. However, this (S)-phenylglycine is described as having an enantiomeric purity of 91.3%, which is not

"pure" as required by the claimed methods. Thus, additional experimentation is needed to achieve the production of enantiomerically pure products using SEQ ID NOs: 2 or 4. Such experimentation is not directed by the specification. The prior art is silent on using SEQ ID NOs: 2 or 4 for the production of enantiomerically pure products and is thus no help in identifying proper conditions, if any such conditions exist. The predictability of such conditions is extremely low, particularly with the inability to alter the enzyme's activity/structure as required in the instant claims.

20. Claims 31-32, 34-37, 44, 49, and 50 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using SEQ ID NOs: 2 or 4 to stereoselectively (>50% ee) produce (S)-phenylglycine from phenylglycinonitrile (or benzaldehyde, KCN, and NH_4Cl), does not reasonably provide enablement for methods producing **any α-substituted carboxylic acid**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make the claimed methods to the full extent of their scope would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The instant specification teaches as described above. No variation of substrates is used in the examples (or are described in the declaration) with SEQ ID NOs: 2 or 4. While nitrilases are known to be somewhat promiscuous enzymes in their substrate specificity, the breadth of the instant claims is virtually boundless, using any aldehyde or ketone. Moreover, not only amino acids are produced within the limitations of the claims, but any α-substituted carboxylic acid.

Even nitrilases have limitations as to their selectivity (see Robertson *et al.* Exploring Nitrilase Sequence Space for Enantioselective Catalysis. Applied and Environmental Microbiology (2004) 70(4): 2429-2436). The predictability of the substrate specificity of SEQ ID NOs: 2 and 4 is very low considering the little information disclosed in the instant specification and the prior art.

21. Claims 24, 38-44, 46, 48, and 50 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using SEQ ID NOs: 2 or 4 to stereoselectively (>50% ee) produce (S)-phenylglycine from phenylglycinonitrile (or benzaldehyde, KCN, and NH_4Cl), does not reasonably provide enablement for methods producing using **sequences related to SEQ ID NOs: 2 or 4 with as little as 70% identity**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. To make the claimed methods to the full extent of their scope would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The only specific description in the instant application of the enzymes of SEQ ID NOs: 2 and 4 is their polypeptide sequences (see Sequence Listing) and their activity on phenylglycinonitrile (see Example 1). No description of how their sequences reflect the nitrilase activity they have. The prior art is relatively silent on the generic structure of nitrilases. Thus, the ability to vary the sequences disclosed and maintain nitrilase activity, in particular stereoselective nitrilase activity, is unpredictable. While the instant specification describes and enables means for identifying other nitrilase genes encoding polypeptides similar to SEQ ID

NOs: 2 and 4 using hybridization methods, etc., these methods do not enable one of skill in the art to make all, or a relevant portion of, the polypeptides used in the methods within the scope of the claims because the ability to find other nitrilases, which is structurally related to SEQ ID NOs: 2 or 4, is not equivalent to the ability to make other nitrilases as required by the statute (i.e., "make and use"). No description in the specification or the art provides particular residues whose encoding is important within the disclosed sequence so that its nitrilase-nature is maintained. Thus, one of skill in the art would be unable to predict the structure of the other members of the genus in order to make such members. Therefore, the instant claims are not enabled to the full extent of their scope.

Response to Arguments

22. Applicant argues the previous enablement rejections of record in their remarks filed July 6, 2004. Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. Applicant argues that no experimentation is necessary to practice the claimed invention because specific sequences are required. If we set aside issues of enablement concerning enantiomeric purity and breadth of product made (and substrate used) by the nitrilases, the breadth of 70% identity having nitrilase activity does require experimentation. One cannot simply randomly mutate the sequence, but directed alteration is required to meet the limitations of the statute ("to make and use" not ---to find---). While conservative substitutions can be routine, not all of these will result in enzymes with the same nitrilase activity. It requires a knowledge of the genus of nitrilase sequences to effectively produce the breadth of the claimed genus without undue experimentation, and this knowledge is not provided by either the specification or the prior art.

Summary of Pending Issues

23. The following is a summary of the issues pending in the instant application:

a) The specification stands objected to under 35 U.S.C. § 132 for containing new matter as filed in the amendment filed July 22, 2003.
b) Claim 1 stands objected to for improper punctuation.
c) Claim 23 stands objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.
d) Claims 1-8, 10, 23, 24, 38-43, 45-46, and 49-50 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "reaction components".
e) Claims 44 and 50 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "the same enzymatic activity as nucleic acid sequence from which it varies".
f) Claims 1-8, 10-17, 23, 24, 33, 38-43, and 45-48 stand rejected under 35 U.S.C. § 112, first paragraph, enablement (enantiomerically pure).
g) Claims 31-32, 34-37, 44, 49, and 50 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement (any α-substituted carboxylic acid).
h) Claims 24, 38-44, 46, 48, and 50 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement (70% identity).

Conclusion

24. Claims 11-8, 10-17, 23, 24, and 31-50 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. The instant Office action is **NON-FINAL**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (571) 272-0931. The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kathleen M Kerr
Primary Examiner
Art Unit 1652

November 21, 2004